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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>4 -32851A/SCR | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/EP 03/14403 | International filing date *(day/month/year)*<br>17.12.2003 | Priority date *(day/month/year)*<br>18.12.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>C07K14/705 | | |
| Applicant<br>NOVARTIS AG et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02.06.2004 | 11.03.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Griesinger, I<br>Telephone No. +49 89 2399-7596 |

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14403

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

| | |
|---|---|
| 1-71 | as originally filed |
| 72-79 | received on 19.04.2004 with letter of 15.04.2004 |

**Claims, Numbers**

| | |
|---|---|
| 1-23 | as originally filed |

**Drawings, Sheets**

| | |
|---|---|
| 1/10-10/10 | as originally filed |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 5-20 (completely), 22 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 5-20 (completely) relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 22 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 3,23 |
| | No: | Claims | 1,2,4,21,22 |
| Inventive step (IS) | Yes: | Claims | 3 |
| | No: | Claims | 1,2,4,21-23 |
| Industrial applicability (IA) | Yes: | Claims | 1-4,21-23 |
| | No: | Claims | 5-20 (opinion reserved) |

2. Citations and explanations

see separate sheet

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

For the reasons indicated in the international search report the subject-matter of claims 11-14,17-20, and 22 does not fulfill the requirements of Articles 5 and 6 PCT. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies (see claim 23).

Claims 5-20 are directed to a method of treatment of the human/animal body. For the assessment of the above-mentioned claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. In other cases, the restriction of the claims to an in vitro method would allow industrial application in view of the EPO.

Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Introduction**

The present communication refers to the following documents (D) cited in the international search report. The numbering will be adhered to during the rest of the procedure.

D1: Jaquemar et al. (1999): "An Ankyrin-like protein with transmembrane domains is specifically lost after oncogenic transformation of human fibroblasts. J. of Biol. Chem. 274, No. 11, pages 7325-7333.

D2: WO 01 18020 A1

D3: Peier et al. (2002): "A TRP channel that senses cold stimuli and menthol. Cell 108, pages 705-715.

D4: Story et al. (2003): "ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112, pages 819-829 (PX-document).

The application relates to nucleic acid sequences of humans, mice, and drosophila encoding a temperature sensitive, non-selective cation channel protein with more than five ankyrin domains, which is activated by temperatures below 20°C, called ANKTM1. The gene was identified by bioinformatic searches for sequences similar to the sequences of known temperature sensors, wherein all known temperature sensors belong to the TRP family of proteins. Subsequently, the protein was expressed transiently, since stable cell lines lost ANTKM1 expression after several passages. The characteristics of the sensor were studied in detail.

D1 discloses a human protein with an amino acid sequence which is 100% identical to the human sequence according to Seq. ID No. 2 and 84.1% identical to the murine sequence (Seq. ID No. 1). By sequence comparison the protein is assumed to be a member of the TRP protein family and to comprise six transmembrane domains, a pore loop and an ankyrin domain. Uncontrolled expression of the encoding gene was not compatible with normal growth of the cell. The protein is supposed to be involved in oncogenic transformation of human fibroblasts.

D2 relates to the cloning and identification of eukaryotic mechanosensory transduction channel. The amino acid sequence of Drosophila melanogaster is 100% identical to Seq. ID No. 4 of the present application.

D3 relates to the identification and cloning of a cold sensor belonging to the TRP protein family. It is a non-selective cation channel gated by cold stimuli and menthol. It is proposed that further such temperature sensors exist.

D4 is the scientific publication corresponding to the present application. The document was published prior to the international filing date but later than the priority date claimed. D4 is not considered in the present communication, since regulations concerning such "PX" documents differ between the PCT member states. However, the document may be relevant for accessing novelty and inventive step of the present application.

## 2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 4, 21, and 22 is not new in the sense of Article 33(2) PCT.

2.1 Claim 2 relates to nucleic acid sequences encoding a temperature sensitive, non-selective cation channel protein with more than five ankyrin domains, which is activated by temperatures below 20°C, called ANKTM1 (for humans Seq. ID No. 2, for mice Seq. ID No. 1, and for drosophila Seq. ID No. 4). Although patenting of a nucleic acid sequence requires disclosure of the function of the sequence in addition to the actual sequence (Rule 23e), the identification of a new function of the sequence can not make the sequence itself novel. Hence, a sequence is only patentable, if the sequence was not known before. However, D1 discloses a human protein with an amino acid sequence which is 100% identical to the human sequence according to Seq. ID No. 2 and D2 discloses an amino acid sequence of Drosophila melanogaster which is 100% identical to Seq. ID No. 4 of the present application. No document discloses a sequence identical to the sequence according to Seq. ID No. 1 of the present application. Hence the subject-matter of claims 2 and 4, which relates to a nucleic acid sequence encoding a protein according to Seq. ID No. 2, is not novel.

2.2 The same considerations apply for the polypeptide according to claim 21.

2.3 Claim 1 defines the nucleic acid sequence by the properties of the encoded protein. The nucleic acid sequence encoding the protein according to Seq. ID No. 2 falls under the scope of the claim. Consequently, the subject-matter of claim 1 is not novel.

2.4 The antibodies according to claim 22 (search and examination were limited to those, see above) are not novel, since D1 already discloses antibodies raised against said protein (page 7326, left-hand column, seventh paragraph to right-hand column, first paragraph).

## 3. Inventive step

3.1 The chimeric or humanized monoclonal antibodies according to claim 23 are not inventive in view of D1 (Article 33(3) PCT), since production of chimeric or humanized antibodies from known antibodies (see previous paragraph) is well known in the art.

3.2 The nucleic acid sequence encoding the channel protein gated by cold stimulus

according to Seq. ID No. 1 as claimed in claim 3 is considered to be inventive.

At the time the present application was filed one gene was known to encode a channel protein gated by cold stimuli (see D3) and several genes were known to encode a channel protein gated by heat. All said temperature-gated channel proteins belong to the TRP protein family. However, the sequence according to Seq. ID No. 1 of the present application does not share a high degree of identity with any of said known proteins. In the prior art, D1 discloses a protein with the highest degree of identity (84.1% identity) with the protein according to Seq. ID No. 1. However, said protein was thought to be involved in oncogenic transformation. Only the present application discloses that the protein is (also) a cold-gated channel protein. Hence, the skilled practitioner looking for a cold-gated channel protein would not consider D1 to be highly relevant and would not try to identify the murine homologue of said gene. In conclusion, the subject-matter of claim 3 is considered to be inventive.

## 4. Further observations

Claims directed to a method of using a protein according to Seq. ID Nos. 1, 2, and 4 or the corresponding nucleic acid sequences could be considered to be novel and inventive, if at least one method step is included which requires the knowledge that the protein functions as a channel gated by cold stimulus.